REMARKS/ARGUMENTS

After entry of this paper, claims 2, 3, 8-10, and 28-31 are pending. Claims 1, 4-7, and 11-12 are canceled in an effort to place the application in condition for allowance. Claims 13-27 are canceled, without prejudice, as being drawn to non-elected subject matter. Claims 8 and 10 are withdrawn. Applicant reserves the right to prosecute any canceled claims and/or subject matter canceled from the claims in a divisional and/or continuation application filed during the pendency of the present application.

New claims 28-31 are added. Support for these claims is found in the specification on page 12, line 17 through page 13, line 17 and page 16, line 28 through page 17, line 21. No new matter is added by these new claims.

Requirement to Elect One (1) Species

The Examiner required Applicants to elect one compound for prosecution in the present application.

As noted above, Applicant affirms the election of 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile as the species. Claims 2, 3, 9, and 28-31 read on the elected species.

35 USC § 112, First Paragraph Rejection

Claims 1-3, 5, 7, and 9 are rejected under 35 USC § 112, first paragraph.

The Examiner alleges that the specification does not provide sufficient guidance or information to enable all compounds of formula I or their tautomers, metabolites, or prodrugs.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. The cancellation of claims 1, 5, and 7 renders the outstanding rejection moot as applied to these claims. Claims 2-3 and 9, which now directly or indirectly depend from new claim 28, remain subject to this rejection.

As noted therein, Examples 8 and 9 are prophetic and are indicative of results to be expected when utilizing the claimed compounds for treating acne and hirsutism.

Example 11 provides data illustrating that 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile has anti-androgenic activity and therefore would be useful in treating acne and hirsutism. Further, one of skill in the art would understand that hirsutism is related to the presence of an excess of androgens and that acne can be related to the same. Therefore, this knowledge in the art combined with the data in Example 11 and the other teachings of the specification on page 28, line 1 through page 39, line 22 would lead one of skill in the art to expect that the compounds of new claim 28 would have anti-androgenic activity and may therefore be utilized in the treatment of acne and hirsutism.

The originally filed specification more than supports embodiments whereby the compounds of the invention are useful in the claimed methods as their metabolites and prodrugs thereof. See, *e.g.*, page 2, lines 18-19; page 12, line 16; page 13, lines 4-5; page 17, lines 1-21; and in the original claims. Further, since these terms were readily understood by one of skill in the art as of the priority date of this application and are readily understand at the present time, definitions for "metabolite" and "prodrug" were not and need not be provided in the instant specification. In fact, Applicant notes that when searches are performed on the Internet in an effort to obtain definitions for the terms "metabolite" and "prodrug", a large number of results are obtained, thereby demonstrating that these terms are well known in the art.

It is well known in the art as of the priority date of this application that the term "pro-drug" includes a chemical compound that converts to another compound *in vivo*. The term "metabolite" includes chemical compounds that are produced when other chemical compounds are subject to metabolic processes of the body. In view thereof, Applicants respectfully assert that the terms "metabolites" and "prodrugs" are adequately described by the specification, thereby satisfying the written description requirement for these terms.

Reconsideration of this rejection is requested.

35 USC § 112, Second Paragraph Rejection

Claims 1-3, 5, 7, and 9 are rejected under 35 USC § 112, second paragraph.

The Examiner alleges that there is insufficient antecedent basis of "(ii)" in claim 1.

The cancellation of claims 1, 5, and 7 and amendment of claims 2-3 and 9 to depend directly or indirectly from new claim 28 renders the outstanding rejection moot.

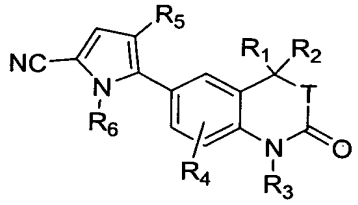
35 USC § 103(a) Rejection

Claims 1-3, 5, 7, and 9 are rejected under 35 USC § 103(a) over International Patent Publication No. WO 00/66581 (Zhang et al.) in view of US Patent No. 6,566,372 (Zhi et al.).

The Examiner asserted that since the androgen and progesterone receptor modulators discussed in Zhi are useful in the treatment of various diseases including hirsutism and acne and that Zhang discusses 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile and that the elected compound of the present invention and that of Zhi have close structural similarity, one of skill in the art would have been motivated to combine these references and make the modification to arrive at the claimed invention.

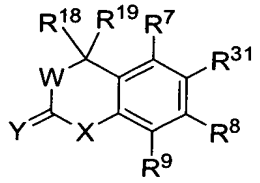
Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason.

Zhang et al. discusses compounds of the following structure:



Zhang permits a large variety of other substituents as noted on pages 9-10. Zhang does not discuss that these compounds could be used for treating acne or hirsutism. Zhang also does not discuss compounds containing S, NR^7, or CR^8R^9 bound to the carbon-atom at the 2-position of the molecule through a double bond.

Zhi et al. discusses compounds of the following structure:



wherein, W is O, among others; X is NR^{16}, among others; Y is S, NR^{16}, or $CR^{16}R^{17}$, among others; and R^{31} is heteroaryl, among others.

If one were to count the number of possibilities of substituents provided by Zhang and/or Zhi, the final number of compounds covered by the same would be sufficiently larger than the seven types of compounds encompassed by the pending claims. See the following summary of the seven types of compounds provided by the pending claims.

(i) $R^{1'}$ is methyl, $R^{2'}$ is methyl, and $R^{3'}$ is C_1 to C_4 alkyl;

(ii) $R^{1'}$ is methyl, $R^{2'}$ is ethyl, and $R^{3'}$ is C_1 to C_4 alkyl;

(iii) $R^{1'}$ is methyl, $R^{2'}$ is CF_3, and $R^{3'}$ is C_1 to C_4 alkyl;

(iv) $R^{1'}$ is ethyl, $R^{2'}$ is ethyl, and $R^{3'}$ is C_1 to C_4 alkyl;

(v) $R^{1'}$ is ethyl, $R^{2'}$ is trifluoromethyl, and $R^{3'}$ is C_1 to C_4 alkyl;

(vi) $R^{1'}$ is CF_3, $R^{2'}$ is CF_3, and $R^{3'}$ is C_1 to C_4 alkyl; and

(vii) $R^{1'}$ and $R^{2'}$ are joined to form a spirocyclic ring containing 3 to 7 carbon atoms and $R^{3'}$ is C_1 to C_4 alkyl.

Further, there is no express teaching in Zhang or Zhi (as required by MPEP 2144.08 (II)(b)) that, when combined, would lead one to select the compound of formula II for treating acne and/or hirsutism. There is absolutely no direction in Zhang or Zhi to select the presently claimed substituents "...in a manner such that the presently claimed compounds would have clearly been obvious to one of ordinary skill in the art". Instead, it is only Applicant that determined that this combination of substituents would be desirable and would be useful in the present invention.

Nor is there any suggestion in the cited documents, when combined, to select the specific substituents of the elected species, i.e., R^1 and R^2 is CH_3, Q^1 is S, R^3 and R^4 are H, R^5 is a pyrrole ring, the pyrrole ring is N-methylated, and the pyrrole ring is substituted with a CN group at the 2-position. The suggestion to select only these

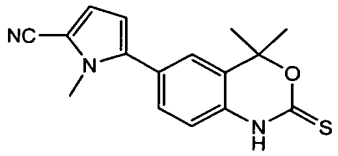
substituents to provide a compound that is useful for treating acne and hirsutism is only provided by the instant specification.

Further, Applicant points to comparative data in the following documents that illustrate that one representative compound of the presently claimed application has better AR antagonistic activity over a cyclothiocarbamate compound having a thiophene group at the 6-position. These documents are enclosed herewith in an Information Disclosure Statement for the Examiner's review and represent work performed by the assignee.

(i) Fensome et al., "Synthesis and Structure-Activity Relationship of Novel 6-Aryl-1,4-Dihydrobenzo[d][1,3]oxazine-2-thiones as Progesterone Receptor Modulators Leading to the Potent and Selective Nonsteroidal Progesterone Receptor Agonists Tanaproget", J. Med. Chem, 48:5092-5095 (2005); and

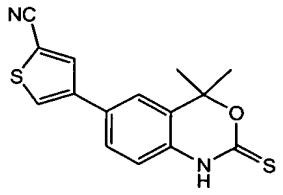
(ii) Zhang et al., "Novel 6-Aryl-1,4-Dihydrobenzo[d][1,3]oxazine-2-thiones as Potent, Selective, and Orally Active Nonsteroidal Progesterone Receptor Agonists", Bioorg. & Med. Chem. Lett., 13:1313-1316 (2003).

Data for the representative compound of the presently claimed application is provided in Fensome. The representative compound tanaproget, i.e., compound 13, demonstrated AR antagonistic activity as evidenced by its IC_{50} value of 131 nM.



Compound 13 (Tanaproget)

Data for a benzoxazin-2-thione compound whereby the substituent at the 6-position is a heterocyclic group other than a pyrrole is provided in Zhang. Specifically, compound 29 had an IC_{50} of 379.0 nM.



Compound 29

These data illustrate that tanaproget is a better AR antagonist than similar benzoxiazin-2-thione compounds having other heterocyclic rings at the 6-position.

Therefore, no combination of Zhang with Zhi can suggest the presently claimed invention.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON

By Cathy A Kodroff

Cathy A. Kodroff
Registration No. 33,980
Suite 210
501 Office Center Drive
Fort Washington, PA 19034
Telephone: (215) 540-9200
Telefacsimile: (215) 540-5818